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U. S. P A T E N T T E X T F I L E

THE WEEKLY PATENT TEXT AND IMAGE DATA IS CURRENT
THROUGH AUGUST 31,1999

* *

=> s (campath)(P)(antibod?)(P)(humanis? or humaniz?)

```
          77 CAMPATH
       36482 ANTIBOD?
         114 HUMANIS?
        1460 HUMANIZ?
L1        21 (CAMPATH)(P)(ANTIBOD?)(P)(HUMANIS? OR HUMANIZ?)
```

=> d l1 1-21 date

L1: 1 of 21

TITLE:	Humanized B-B10		
US PAT NO:	5,886,152 [IMAGE AVAILABLE]	DATE ISSUED:	Mar. 23, 1999
APPL-NO:	08/232,081	DATE FILED:	May 10, 1994
FRN-PR. NO:	3-323319	FRN FILED:	Dec. 6, 1991
FRN-PR. CO:	Japan		
PCT-NO:	PCT/JP92/01583	PCT-FILED:	Dec. 3, 1992
		371-DATE:	May 10, 1994
		102(E)-DATE:	May 10, 1994
PCT-PUB-NO:	WO93/11238	PCT-PUB-DATE:	Jun. 10, 1993

L1: 2 of 21

TITLE:	Methods and materials for modulation of the immunosuppressive activity and toxicity of monoclonal antibodies		
US PAT NO:	5,885,573 [IMAGE AVAILABLE]	DATE ISSUED:	Mar. 23, 1999
APPL-NO:	08/070,116	DATE FILED:	Jun. 1, 1993

L1: 3 of 21

TITLE:	Production of antibodies		
US PAT NO:	5,876,961 [IMAGE AVAILABLE]	DATE ISSUED:	Mar. 2, 1999
APPL-NO:	08/378,939	DATE FILED:	Jan. 26, 1995
FRN-PR. NO:	9115284	FRN FILED:	Jul. 15, 1991
FRN-PR. CO:	United Kingdom		
FRN-PR. NO:	9206284	FRN FILED:	Mar. 23, 1992
FRN-PR. CO:	United Kingdom		
FRN-PR. NO:	9116594	FRN FILED:	Aug. 1, 1994
FRN-PR. CO:	United Kingdom		
REL-US-DATA:	Continuation of Ser. No. 952,640, Dec. 1, 1992, abandoned.		

L1: 4 of 21

TITLE:	Humanized monoclonal antibodies against human interleukin-4		
US PAT NO:	5,863,537 [IMAGE AVAILABLE]	DATE ISSUED:	Jan. 26, 1999
APPL-NO:	08/290,793	DATE FILED:	Aug. 16, 1994
PCT-NO:	PCT/US93/01301	PCT-FILED:	Feb. 18, 1993
		371-DATE:	Aug. 16, 1994
		102(E)-DATE:	Aug. 16, 1994
PCT-PUB-NO:	WO93/17106	PCT-PUB-DATE:	Sep. 2, 1993
REL-US-DATA:	Continuation-in-part of Ser. No. 841,659, Feb. 19, 1992, abandoned.		

L1: 5 of 21

TITLE:	Preparation of chimaeric antibodies using the recombinant PCR strategy		
US PAT NO:	5,858,725 [IMAGE AVAILABLE]	DATE ISSUED:	Jan. 12, 1999
APPL-NO:	08/039,198	DATE FILED:	Jul. 29, 1993
FRN-PR. NO:	9022011	FRN FILED:	Oct. 10, 1990

FRN-PR. CO: United Kingdom
PCT-NO: PCT/GB91/[redacted]44 PCT-FILED: Oc[redacted]8, 1990
371-DATE: Jul. 29, 1993
102(E)-DATE: Jul. 29, 1993
PCT-PUB-NO: WO92/07075 PCT-PUB-DATE: Apr. 30, 1992

L1: 6 of 21

TITLE: Process for improving the stability of antibodies
US PAT NO: 5,854,027 DATE ISSUED: Dec. 29, 1998
[IMAGE AVAILABLE]
APPL-NO: 08/765,179 DATE FILED: Jan. 14, 1997
FRN-PR. NO: 44 25 115.7 FRN FILED: Jul. 15, 1994
FRN-PR. CO: Federal Republic of Germany
PCT-NO: PCT/EP95/02626 PCT-FILED: Jul. 5, 1995
371-DATE: Jan. 14, 1997
102(E)-DATE: Jan. 14, 1997
PCT-PUB-NO: WO96/02574 PCT-PUB-DATE: Feb. 1, 1996

L1: 7 of 21

TITLE: Antibodies to the antigen campath-1
US PAT NO: 5,846,534 DATE ISSUED: Dec. 8, 1998
[IMAGE AVAILABLE]
APPL-NO: 08/235,705 DATE FILED: Apr. 29, 1994
FRN-PR. NO: 8803228 FRN FILED: Feb. 12, 1988
FRN-PR. CO: United Kingdom
FRN-PR. NO: 8804464 FRN FILED: Feb. 25, 1988
FRN-PR. CO: United Kingdom
REL-US-DATA: Continuation of Ser. No. 99,480, Jul. 30, 1993, abandoned, which is a continuation of Ser. No. 921,601, Aug. 3, 1992, abandoned, which is a continuation of Ser. No. 424,233, Oct. 12, 1989, abandoned.

L1: 8 of 21

TITLE: Immunoglobulin variants
US PAT NO: 5,821,337 DATE ISSUED: Oct. 13, 1998
[IMAGE AVAILABLE]
APPL-NO: 07/934,373 DATE FILED: Aug. 21, 1992
REL-US-DATA: Continuation-in-part of Ser. No. 715,272, Jun. 14, 1991, abandoned.

L1: 9 of 21

TITLE: Monoclonal antibodies and FV specific for CD2 antigen
US PAT NO: 5,807,734 DATE ISSUED: Sep. 15, 1998
[IMAGE AVAILABLE]
APPL-NO: 08/456,221 DATE FILED: May 31, 1995
REL-US-DATA: Division of Ser. No. 68,946, May 25, 1993.

L1: 10 of 21

TITLE: Monoclonal antibodies and FV specific for CD2 antigen
US PAT NO: 5,795,572 DATE ISSUED: Aug. 18, 1998
[IMAGE AVAILABLE]
APPL-NO: 08/068,946 DATE FILED: May 25, 1993

L1: 11 of 21

TITLE: Method for stabilizing immunoglobulin compositions
US PAT NO: 5,792,838 DATE ISSUED: Aug. 11, 1998
[IMAGE AVAILABLE]
APPL-NO: 08/465,319 DATE FILED: Jun. 5, 1995
FRN-PR. NO: 9122820 FRN FILED: Oct. 28, 1991
FRN-PR. CO: United Kingdom
REL-US-DATA: Continuation of Ser. No. 232,127, Apr. 28, 1994.

L1: 12 of 21

TITLE: Recombinant CDw52 antigen
US PAT NO: 5,786,176 DATE ISSUED: Jul. 28, 1998
[IMAGE AVAILABLE]

APPL-NO: 08/374,533
FRN-PR. NO: 9215071
FRN-PR. CO: United Kingdom
PCT-NO: PCT/GB93/01482

DATE FILED: Feb. 3, 1995
FRN FILED: Jul. 15, 1992

PCT-FILED: Jul. 14, 1993
371-DATE: Feb. 3, 1995
102(E)-DATE: Feb. 3, 1995

PCT-PUB-NO: WO94/02604
PCT-PUB-DATE: Feb. 3, 1994

L1: 13 of 21

TITLE: Cloning and exprssion of humanized monoclonal antibodies against human interluekin-4

US PAT NO: 5,770,403 [IMAGE AVAILABLE]
DATE ISSUED: Jun. 23, 1998

APPL-NO: 08/469,557
DATE FILED: Jun. 6, 1995

REL-US-DATA: Division of Ser. No. 290,793, Aug. 16, 1994, which is a continuation of Ser. No. 841,659, Feb. 19, 1992, abandoned.

L1: 14 of 21

TITLE: Humanized monoclonal antibodies against human interleukin-4

US PAT NO: 5,705,154 [IMAGE AVAILABLE]
DATE ISSUED: Jan. 6, 1998

APPL-NO: 08/704,744
DATE FILED: Sep. 6, 1996

PCT-NO: PCT/US95/02400
PCT-FILED: Mar. 8, 1995
371-DATE: Sep. 6, 1996
102(E)-DATE: Sep. 6, 1996

PCT-PUB-NO: WO95/24481
PCT-PUB-DATE: Sep. 14, 1995

L1: 15 of 21

TITLE: Immunoglobulins stabilized with a chelator of copper ions

US PAT NO: 5,654,403 [IMAGE AVAILABLE]
DATE ISSUED: Aug. 5, 1997

APPL-NO: 08/232,127
DATE FILED: Apr. 28, 1994

FRN-PR. NO: 9122820
FRN FILED: Oct. 28, 1991

FRN-PR. CO: United Kingdom

PCT-NO: PCT/GB92/01970
PCT-FILED: Oct. 27, 1992
371-DATE: Apr. 28, 1994
102(E)-DATE: Apr. 28, 1994

PCT-PUB-NO: WO93/08837
PCT-PUB-DATE: May 13, 1993

L1: 16 of 21

TITLE: Purified immunoglobulin

US PAT NO: 5,644,036 [IMAGE AVAILABLE]
DATE ISSUED: Jul. 1, 1997

APPL-NO: 08/319,598
DATE FILED: Oct. 7, 1994

FRN-PR. NO: 9022547-5
FRN FILED: Oct. 17, 1990

FRN-PR. CO: United Kingdom

REL-US-DATA: Continuation of Ser. No. 304,440, Sep. 12, 1994, which is a continuation of Ser. No. 985,272, Dec. 3, 1992, abandoned, which is a continuation of Ser. No. 975,967, Nov. 13, 1992, abandoned, which is a continuation of Ser. No. 777,731, Oct. 16, 1991.

L1: 17 of 21

TITLE: Method for culturing Chinese hamster ovary cells

US PAT NO: 5,633,162 [IMAGE AVAILABLE]
DATE ISSUED: May 27, 1997

APPL-NO: 08/205,379
DATE FILED: Mar. 4, 1994

FRN-PR. NO: 9022545
FRN FILED: Oct. 17, 1990

FRN-PR. CO: United Kingdom

REL-US-DATA: Continuation of Ser. No. 991,717, Dec. 18, 1992, Pat. No. 5,316,938, which is a continuation of Ser. No. 777,729, Oct. 16, 1991, abandoned.

L1: 18 of 21

TITLE: Humanized monoclonal antibodies against human interleukin-4
US PAT NO: 5,597,710 [IMAGE AVAILABLE] DATE ISSUED: Jan. 28, 1997
APPL-NO: 08/208,886 DATE FILED: Mar. 10, 1994

L1: 19 of 21

TITLE: Production of chimeric antibodies - a combinatorial approach
US PAT NO: 5,565,332 [IMAGE AVAILABLE] DATE ISSUED: Oct. 15, 1996
APPL-NO: 08/211,202 DATE FILED: Jun. 24, 1994
FRN-PR. NO: 9120252 FRN FILED: Sep. 23, 1991
FRN-PR. CO: United Kingdom
FRN-PR. NO: 9120377 FRN FILED: Sep. 25, 1991
FRN-PR. CO: United Kingdom
FRN-PR. NO: 9206318 FRN FILED: Mar. 24, 1992
FRN-PR. CO: United Kingdom
FRN-PR. NO: 9206372 FRN FILED: Mar. 24, 1992
FRN-PR. CO: United Kingdom
PCT-NO: PCT/GB92/01755 PCT-FILED: Sep. 23, 1992
371-DATE: Jun. 24, 1994
102(E)-DATE: Jun. 24, 1994
PCT-PUB-NO: WO93/06213 PCT-PUB-DATE: Apr. 1, 1993

L1: 20 of 21

TITLE: CDR grafted humanised chimeric T-cell antibodies
US PAT NO: 5,502,167 [IMAGE AVAILABLE] DATE ISSUED: Mar. 26, 1996
APPL-NO: 08/244,626 DATE FILED: Jul. 15, 1994
FRN-PR. NO: 9125979 FRN FILED: Dec. 6, 1991
FRN-PR. CO: United Kingdom
PCT-NO: PCT/GB92/02251 PCT-FILED: Dec. 4, 1992
371-DATE: Jun. 3, 1994
102(E)-DATE: Jun. 3, 1994
PCT-PUB-NO: WO93/11237 PCT-PUB-DATE: Jun. 10, 1993

L1: 21 of 21

TITLE: Defined media for serum-free tissue culture
US PAT NO: 5,316,938 [IMAGE AVAILABLE] DATE ISSUED: May 31, 1994
APPL-NO: 07/991,717 DATE FILED: Dec. 18, 1992
FRN-PR. NO: 9022545 FRN FILED: Oct. 17, 1990
FRN-PR. CO: United Kingdom
REL-US-DATA: Continuation of Ser. No. 777,729, Oct. 16, 1991, abandoned.

=> s l1/clm

3 CAMPATH/CLM
9638 ANTIBOD?/CLM
8 HUMANIS?/CLM
151 HUMANIZ?/CLM
L2 0 ((CAMPATH/CLM)(P)(ANTIBOD?/CLM)(P)(HUMANIS?/CLM OR HUMANIZ?/CLM))

=> d l1 1-21 kwic

US PAT NO: 5,886,152 [IMAGE AVAILABLE] L1: 1 of 21

SUMMARY:

BSUM(12)

For . . . MAb V regio[redacted] by the use of site specific mut[redacted]ion with a long oligonucleotide. As[redacted] example of obtaining a **humani[redacted] antibody** as explained above, there is known an attempt for **humanization** of rat MAb **Campath**-1 recognizing CDw52 antigen on human T calls (EP-A-89301291).

DETDESC:

DETD(26)

3) Antigenicity of **humanized** B-B10 is much less than mouse B-B10. As a matter of fact, administration of **humanized antibody**, **Campath**-1H, did not induce anti-**Campath**-1H **antibody** in two instances (Lancet, Vol.2, 1394, 1988).

US PAT NO: 5,885,573 [IMAGE AVAILABLE] L1: 2 of 21

SUMMARY:

BSUM(8)

A major concern is that the **humanized antibody** will still be immunogenic because of the presence of the non-CDR residues which need to be transferred in order to regenerate suitable antigen binding activity, in addition to any antiparatope **antibodies** that may be generated. To date two **humanized antibodies**, **CAMPATH**-1H and Hu2PLAP, have been administered to patients (LoBuglio, 1989). Both of these **antibodies** used the rodent amino acid sequences in complementarity determining regions (CDRs) as defined by Kabat (1987), along with the rodent. . . predicted to be solvent accessible near CDR1. In both cases no specific immune response to initial treatments with the administered **antibody** was noted, although responses to a second course of treatment was seen in one study using **CAMPATH**-1H for the treatment of rheumatoid arthritis (Frenken, 1991). There have been no reported clinical studies using **humanized antibodies** in which other non-CDR solvent-accessible residues have also been included in the design.

US PAT NO: 5,876,961 [IMAGE AVAILABLE] L1: 3 of 21

DETDESC:

DETD(44)

The light chain probes were human lambda cDNA (**humanised** anti-CD3 mAb .lambda. L chain insert [rat anti-CD3 mAb L chain CDR's reshaped an human .lambda. Kern.sup.- Oz.sup.- Ab L chain: E Routledge Eur.J.Immunol. 1991; 21:2717) and (a **Campath**-1H .kappa. L chain cDNA insert (rat **Campath** 1 mAb L chain CDR's reshaped on human REI .kappa. AB L chain; Page and Sydenham Bio/technology 1991; 9:64;) which. . . DNA Labelling and Detection Kit (Boehringer Mannheim, Lewes, UK) and employed to screen filters, possessing approximately 4000 lifted colonies, for **antibody** D light chain following the manufacturer's protocol. Twenty potential positive colonies were detected and 10 selected for further analysis. Plasmid. . . FRG) or the method of Del Sal et al. (1988) and 8 contained inserts of the expected size for human **antibody** light chain cDNA. A clone, pH210L2, was selected, and sequenced in both directions by plasmid priming following the dideoxy chain. . .

US PAT NO: 5,863,537 [IMAGE AVAILABLE] L1: 4 of 21

DETDESC:

DETD(235)

The . . . SalI site followed by a translational initiation sequence (Kozak, supra) and a sequence encoding the leader peptide corresponding to the anti-**CAMPATH**-1 **antibodies** (Reichmann et al., supra). The fragment 1 sequence extended through a SmaI site and included the coding sequence for amino acid residues 1-42 of the variable region of the **humanized** heavy chain.

US PAT NO: 5,858,725 [IMAGE AVAILABLE] L1: 5 of 21

SUMMARY:

BSUM(4)

The preparation of an altered **antibody** in which the CDRs are derived from a different species to the variable domain framework regions is disclosed in EP-A-0239400. The CDRs may be derived from a rat or mouse monoclonal **antibody**. The framework of the variable domains, and the constant domains, of the altered **antibody** may be derived from a human **antibody**. Such a **humanised antibody** elicits a negligible immune response when administered to a human compared to the immune response mounted by a human against a rat or mouse **antibody**. **Humanised CAMPATH**-1 **antibody** is disclosed in EP-A-0328404.

US PAT NO: 5,854,027 [IMAGE AVAILABLE] L1: 6 of 21

SUMMARY:

BSUM(3)

Antibody biotechnology is a rapidly expanding field with focus on diagnostics (in vitro: e.g. antigen detection, in vivo: e.g. imaging) in therapy (in this case particularly **humanized antibodies** with increased serum half-life and reduced immunogenicity) and in toxicology (e.g. anti-digoxin **antibodies** as a specific antidote for a cardiac glycoside overdose). Further areas of application are under development for the induction of transplant tolerance (e.g. by anti-CD4 AB), for immunotherapy (e.g. **CAMPATH** in non-Hodgkin lymphoma) and for catalytic **antibodies** which in particular enable stereoselective and regioselective catalysis.

US PAT NO: 5,846,534 [IMAGE AVAILABLE] L1: 7 of 21

DETDESC:

DETD(46)

The rat **antibody** and fully **humanised antibody** were compared in a direct binding assay to **Campath**-1 antigen. **Antibody** concentrations were determined as described in FIGS. 7 and 8. The amount of rat **antibody** bound to partially purified **Campath**-1 antigen was determined as described in connection with Table 1. The amount of human **antibody** bound was determined by an ELISA assay using a biotinylated sheep anti-human IgG **antibody** (Amersham).

US PAT NO: 5,821,337 [IMAGE AVAILABLE] L1: 8 of 21

SUMMARY:

BSUM(11)

The therapeutic promise of this approach is supported by the clinical efficacy of a **humanized antibody** specific for the **CAMPATH**-1 antigen with two non-Hodgkin lymphoma patients, one of whom had previously developed an anti-globulin response to the parental rat **antibody** (Riechmann, L. et al, Nature 332: 323-327 (1988); Hale, G. et al., Lancet 1: 1394-1399 (1988)). A murine **antibody** to the

interleukin 2 receptor has also recently been **humanized** (Queen, C. et al., Proc. Natl. Acad Sci USA 86: 10029-10033 (1989)) as potential immunosuppressive reagent. Additional references related to **humanization** of **antibodies** include Co et al., Proc. Natl. Acad. Sci. USA 88: 2869-2873 (1991); Gorman et al., Proc. Natl. Acad. Sci. USA. . .

US PAT NO: 5,807,734 [IMAGE AVAILABLE] L1: 9 of 21

DETDESC:

DETD(31)

Among the preferred **antibodies** useful for suppressing HIV-1 production and CD4.sup.+ lymphocytes is a chimeric **humanized** single-chain **antibody** designated CD2 SFv-Ig. The use of chimeric monoclonal **antibodies** is generally preferable in the treatment of human subjects because such monoclonal **antibodies**: (1) may induce less of a anti-murine immune response and (2) may have a longer survival time in vivo (G. Hale et al., "Remission Induction in Non-Hodgkin Lymphoma With Reshaped Human Monoclonal **Antibody CAMPATH**-1H," Lancet 2:1394-1399 (1988); D. Yasmeen et al., "The Structure and Function of Immunoglobulin Domains. IV. The Distribution of Some Effector. . .

US PAT NO: 5,795,572 [IMAGE AVAILABLE] L1: 10 of 21

DETDESC:

DETD(31)

Among the preferred **antibodies** useful for suppressing HIV-1 production and CD4.sup.+ lymphocytes is a chimeric **humanized** single-chain **antibody** designated CD2 SFv-Ig. The use of chimeric monoclonal **antibodies** is generally preferable in the treatment of human subjects because such monoclonal **antibodies**: (1) may induce less of a anti-murine immune response and (2) may have a longer survival time in vivo (G. Hale et al., "Remission Induction in Non-Hodgkin Lymphoma With Reshaped Human Monoclonal **Antibody CAMPATH**-1H," Lancet 2: 1394-1399 (1988); D. Yasmeen et al., "The Structure and Function of Immunoglobulin Domains. IV. The Distribution of Some. . .

US PAT NO: 5,792,838 [IMAGE AVAILABLE] L1: 11 of 21

SUMMARY:

BSUM(19)

The invention finds particular application in the stabilisation of recombinant **antibodies**, most particularly chimeric **antibodies** or **humanised** (CDR-grafted) **antibodies**. Particular examples of these include chimeric or **humanised antibodies** against CD2, CD3, CD4, CD5, CD7, CD8, CD11a,b, CD18, CD19, CD25, CD33, CD54 and especially **humanised antibodies** against the CDw52 antigen, such as **CAMPATH**-1H (**CAMPATH** is a Trade Mark of the Wellcome group of companies). Further examples include chimeric or **humanised antibodies** against various tumour cell marker antigens.

SUMMARY:

BSUM(23)

Immunoglobulins . . . preparation will be reconstituted to contain, an effective therapeutic dose of the immunoglobulin per unit dose. the case of the **humanised antibody CAMPATH**-1H, liquid formulations or reconstituted lyophilised formulations preferably contain 0.5 to 20 mg/ml of the **antibody**, preferably 2 mg/ml or 10 mg/ml.

DETDESC:

DETD(2)

The effect of various additives on the stability of a recombinant **antibody** was studied at 37.degree. C. The **antibody** was **CAMPATH** 1H, a **humanised antibody** against the CDw52 antigen (Riechmann et al, Nature, 322, 323-327 (1988)), which had been produced by expression in a recombinant CHO cell line transformed with DNA encoding the heavy and light chains of the **antibody** molecule. The **antibody** was extracted from the cell culture medium and purified and was then stored as a solution (1 mg/ml) in phosphate. . .

DETDESC:

DETD(44)

. . .

9

	% Peak C			
	4.degree. C.	62.degree. C.	62.degree. C. +	62.degree. C. +
Antibody	No EDTA	No EDTA	Cu.sup.2+	EDTA
IgG1	0.54	1.58	5.59	1.1
C1H	0	2.49	27.98	0
CD4	0.4	1.91	21.52	1.84
IgG2	0	1.81	3.77	0

IgG1 = mouse monoclonal IgG.sub.1 **antibody**, 1 mg/ml in phosphate buffered saline;
C1H = **CAMPATH** 1H of the type described in Example 1, 1 mg/ml in phosphate buffered saline;
CD4 = **Humanised** antiCD4 monoclonal **antibody** having the same framework region as **CAMPATH** 1H and produced in CHO cells, 1 mg/ml in phosphate buffered saline;
IgG2 = Mouse IgG.sub.2 monoclonal **antibody** I4139 commercially from Sigma, supplied lyophilised from phosphate buffer and redissolved with water to mg/ml.

US PAT NO: 5,786,176 [IMAGE AVAILABLE] L1: 12 of 21

SUMMARY:

BSUM(31)

The recombinant CDw52 antigen according to the invention may be used to develop simple and reliable assays for the concentration of **antibodies** recognising this antigen. As noted above **antibodies** against the CDw52 antigen, such as the **humanised antibody** **Campath** 1H, are being developed for use in a number of therapeutic applications. Accordingly, assays for such **antibodies** will be needed in a number of situations including quality control tests during the production of the **antibody** and the measurement of serum levels of the **antibody** during therapy.

SUMMARY:

BSUM(41)

The recombinant antigen may be used in the purification of any **antibody** recognising the CDw52 (**Campath** 1) antigen, for example the **humanised antibody Campath** 1H. The recombinant antigen may be coupled to a solid support and a crude preparation of the **antibody** passed over it. Only the **antibody** recognising the CDw52 antigen should bind and the **antibody** can then be eluted by a change in conditions, for example a pH shift. Suitable crude **antibody** preparations include medium resulting from the growth of a recombinant cell line, for example a mammalian cell line, producing the **antibody** in question.

US PAT NO: 5,770,403 [IMAGE AVAILABLE] L1: 13 of 21

DETDESC:

DETD(235)

The . . . SalI site followed by a translational initiation sequence (Kozak, supra) and a sequence encoding the leader peptide corresponding to the anti-**CAMPATH**-1 **antibodies** (Reichmann et al., supra). The fragment 1 sequence extended through a SmaI site and included the coding sequence for amino acid residues 1-42 of the variable region of the **humanized** heavy chain.

US PAT NO: 5,705,154 [IMAGE AVAILABLE] L1: 14 of 21

DETDESC:

DETD(193)

The . . . SalI site followed by a translational initiation sequence (Kozak, supra) and a sequence encoding the leader peptide corresponding to the anti-**CAMPATH**-1 **antibodies** (Reichmann et al., supra). The fragment 1 sequence extended through a SmaI site and included the coding sequence for amino acid residues 1-42 of the variable region of the **humanized** heavy chain.

US PAT NO: 5,654,403 [IMAGE AVAILABLE] L1: 15 of 21

SUMMARY:

BSUM(19)

The invention finds particular application in the stabilisation of recombinant **antibodies**, most particularly chimeric **antibodies** or **humanised** (CDR-grafted) **antibodies**. Particular examples of these include chimeric or **humanised antibodies** against CD2, CD3, CD4, CD5, CD7, CD8, CD11a,b, CD18, CD19, CD25, CD33, CD54 and especially **humanised antibodies** against the CDw52 antigen, such as **CAMPATH**-1H (**CAMPATH** is a Trade Mark of the Wellcome group of companies). Further examples include chimetic or **humanised antibodies** against various tumour cell marker antigens.

SUMMARY:

BSUM(23)

Immunoglobulins . . . will be reconstituted to contain, an effective therapeutic dose of the immunoglobulin per unit dose. In the case of the **humanised antibody CAMPATH**-1H, liquid formulations or reconstituted lyophilised formulations preferably contain 0.5 to 20 mg/ml of the **antibody**, preferably 2 mg/ml or 10 mg/ml.

DETDESC:

DETD(3)

The effect of various additives on the stability of a recombinant **antibody** was studied at 37.degree. C. The **antibody** was **CAMPATH** 1H, a **humanised antibody** against the CDw52 antigen (Riechmann et al, Nature, 332, 323-327 (1988)), which had been produced by expression in a recombinant CHO cell line transformed with DNA encoding the heavy and light chains of the **antibody** molecule. The **antibody** was extracted from the cell culture medium and purified and was then stored as a solution (1 mg/ml) in phosphate. . .

DETDESC:

DETD(45)

TABLE 9

	% Peak C			
	4.degree. C.	62.degree. C.	62.degree. C.	62.degree. C.
Antibody	No EDTA	No EDTA	+ Cu.sup.2+ + EDTA	
IgG1	0.54	1.58	5.59	1.1
C1H	0	2.49	27.98	0
CD4	0.4	1.91	21.52	1.84
IgG2	0	1.81	3.77	0

IgG1 = mouse monoclonal IgG.sub.1 **antibody**, 1 mg/ml in phosphate buffered saline;
C1H = **CAMPATH** 1H of the type described in Example 1, 1 mg/ml in phosphate buffered saline;
CD4 = **Humanised** antiCD4 monoclonal **antibody** having the same framework region as **CAMPATH** 1H and produced in CHO cells, 1 mg/ml in phosphate buffered saline;
IgG2 = Mouse IgG.sub.2 monoclonal **antibody** I4139 commercially available from Sigma, supplied lyophilised from phosphate buffer and redissolved with water to 1 mg/ml.

US PAT NO: 5,644,036 [IMAGE AVAILABLE] L1: 16 of 21

SUMMARY:

BSUM(5)

The . . . not haemopoietic cells, nor is it expressed on granulocytes, platelets, erythroid or myeloid bone marrow cells. A number of monoclonal **antibodies** of different isotypes have been raised against this antigen and reported in the literature, (G. Hale et al Tissue Antigens, 1990, 35, pp 118-127). One of these **antibodies**, an IgG1 **antibody**, has been **humanised** (Nature, 1988, 322, 323-327 and EP0328404). This **antibody** is known as **Campath** 1H (**Campath** is a trademark of The Wellcome Foundation Ltd). A preparation of this **antibody** has been used to treat patients suffering from Non Hodgkins' lymphoma, (G. Hale et al, Lancet, 1988, pp 1394-1399).

SUMMARY:

BSUM(37)

Accordingly the purified anti-CD.sub.w 52 **antibody** of the invention may be a rat, mouse or human **antibody** wherein the amino acid sequences of the heavy and light chains are homologous with those sequences of **antibody** produced by the species lymphocytes in vivo or in vitro by hybridomas. Preferably the anti-CDw52 **antibody** is an altered **antibody** such as a hybrid **antibody** in which the heavy and light chains are homologous to a natural **antibody** but are combined in a way that would not occur naturally. The **antibody** may be chimaeric **antibody** which has variable regions from one **antibody** and constant regions from another. Thus, chimaeric **antibodies** may be species/species chimaeras or class/class chimaeras. Such chimaeric **antibodies** may have one or more further modifications to improve antigen binding ability or to alter effector functioning. Another form of altered **antibody** is a **humanised** or CDR-grafted **antibody** including a composite **antibody**, wherein parts of the hypervariable regions in addition to the CDRs are transferred to the human framework. Additional amino acids in the framework or constant regions of such **antibodies** may be altered. Thus within the scope of the invention is included, any anti-CDw52 altered **antibody** in which the amino acid sequence is not one which exists in nature. However, CDR-grafted **antibodies** are most preferred of which **Campath** 1H (Trademark of The Wellcome Foundation Ltd.) is an example. The **antibody** chain DNA sequences including the CDRs of **Campath** 1H are set out in EPO328404, the disclosure of which is hereby incorporated by reference. The invention therefore includes a purified preparation of an anti-CDw52 **antibody** wherein the **antibody** comprises one or more of the CDR sequences set out in EPO328404.

US PAT NO: 5,633,162 [IMAGE AVAILABLE] L1: 17 of 21

SUMMARY:

BSUM(37)

The medium is preferred for the production of all types of **antibodies** natural and altered. The invention therefore includes production of human **antibodies** wherein the amino acid sequences of the heavy and light chains are homologous with those sequences of **antibodies** produced by human lymphocytes in vivo or in vitro by hybridomas. Also provided are hybrid **antibodies** in which the heavy and light chains are homologous to a natural **antibody** but are combined in a way that would not occur naturally. For example, a bispecific **antibody** has antigen binding sites specific to more than one antigen. The constant region of the **antibody** may relate to one or other of the antigen binding regions or may be from a further **antibody**. Altered **antibodies**, for example chimaeric **antibodies** have variable regions from one **antibody** and constant regions from another. Thus, chimaeric **antibodies** may be species/species chimaeras or class/class chimaeras. Such chimaeric **antibodies** may have one or more further modifications to improve antigen binding ability or to alter effector functioning. **Humanised** or CDR-grafted **antibodies** (EP 239400) are embraced within the invention, in particular **Campath** 1H (EP328404) (**Campath** is a TM of The Wellcome Foundation) also composite **antibodies**, wherein parts of the hypervariable regions in addition to the CDRs are tranferred to the human framework. Additional amino acids in the framework or constant regions of such **antibodies** may be altered. The invention further includes the production of Feb fragments which are roughly equivalent to the Y branch. . .

DETDESC:

DETD(12)

C1H . . . 77, 7 pp 4216-4220). CHO DUK B11 cells cannot produce

dihydrofolate reductase (dhfr). These cells were engineered to produce a **humanised** IgG **antibody**, **Campath** 1H (Winter et al., Nature, 1988, 322, 323-327), using plasmid constructs to express heavy and light **antibody** chains and the mouse dhfr. Expression is amplified and maintained using the folate antagonist methotrate. C1H 3D11* cells growing as. . .

US PAT NO: 5,597,710 [IMAGE AVAILABLE] L1: 18 of 21

DETDESC:

DETD(186)

The . . . SalI site followed by a translational initiation sequence (Kozak, supra) and a sequence encoding the leader peptide corresponding to the anti-**CAMPATH**-1 **antibodies** (Reichmann et al., supra). The fragment 1 sequence extended through a SmaI site and included the coding sequence for amino acid residues 1-42 of the variable region of the **humanized** heavy chain.

US PAT NO: 5,565,332 [IMAGE AVAILABLE] L1: 19 of 21

SUMMARY:

BSUM(3)

To overcome these problems, Winter and colleagues (GB2188638B) developed a method of **humanising** or "reshaping` such **antibodies**. The complementarity determining regions (CDRs) of the mouse **antibody**, which comprise the antigen combining site, are inserted into human framework regions thereby generating **antibodies** in which only the CDR sequences are derived from the original mouse **antibody**. This is the technique known as "CDR-grafting" or "CDR-imprinting". One such reshaped **antibody CAMPATH**-1 (L. Riechmann et al, 1988 Nature 332, pp323-327 has been used successfully in the treatment of B cell lymphoma (G.. . . Med. 1990 323, pp250-254) and rheumatoid arthritis (V. Kyle et at 1991 J. Rheumatol. 18, pp1737-1738). This has prompted the **humanisation** of a large number of **antibodies** for therapeutic purposes directed against cancer markers, for example the interleukin 2 receptor (C. Queen et al, 1989 Proc. Natl.. . . Sci. USA 89, pp4285-4289) and carcinoembryonic antigen (K. Bosslet et al. Brit. J. Cancer 65, pp234-238, 1992). A number of **antibodies** directed against infectious viruses have also been **humanised**, for instance **antibodies** directed against respiratory syncytial virus (P. R. Tempest et al, 1991 Bio/Technology 9, pp266-271); herpes simplex virus (M. S. Co. . . et al 1991 Proc. Natl. Acad. Sci. USA 88, pp2869-2873) and human immunodeficiency virus (H. Maeda et al 1991 Human **Antibodies** and Hybridomas 2, pp124-134). **Humanised antibodies** have also been used for imaging tumours after labelling with radioisotopes (V. Hird et al, 1991 Brit. J. Cancer 64. . .

US PAT NO: 5,502,167 [IMAGE AVAILABLE] L1: 20 of 21

SUMMARY:

BSUM(4)

The preparation of an altered **antibody** in which the CDRs are derived from a different species than the framework of the **antibody**'s variable domains is disclosed in EP-A-0239400. The CDRs may be derived from a rat or mouse monoclonal **antibody**. The framework of the variable domains, and the constant domains, of the altered **antibody** may be derived from a human **antibody**. Such a **humanised antibody** elicits a negligible immune response when administered to a human compared to the immune response mounted by a human against a rat or mouse **antibody**. **Humanised CAMPATH**-1 **antibody** (**Campath**

is a Trademark of The Wellcome Foundation Ltd.) is disclo in EP-A-0328404.

US PAT NO: 5,316,938 [IMAGE AVAILABLE] L1: 21 of 21

SUMMARY:

BSUM(36)

The medium is preferred for the production of all types of **antibodies** natural and altered. The invention therefore includes production of human **antibodies** wherein the amino acid sequences of the heavy and light chains are homologous with those sequences of **antibodies** produced by human lymphocytes in vivo or in vitro by hybridomas. Also provided are hybrid **antibodies** in which the heavy and light chains are homologous to a natural **antibody** but are combined in a way that would not occur naturally. For example, a bispecific **antibody** has antigen binding sites specific to more than one antigen. The constant region of the **antibody** may relate to one or other of the antigen binding regions or may be from a further **antibody**. Altered **antibodies**, for example chimaeric **antibodies** have variable regions from one **antibody** and constant regions from another. Thus, chimaeric **antibodies** may be species/species chimaeras or class/class chimaeras. Such chimaeric **antibodies** may have one or more further modifications to improve antigen binding ability or to alter effector functioning. **Humanised** or CDR-grafted **antibodies** (EP 239400) are embraced within the invention, in particular **Campath** 1H (EP328404) (**Campath** is a TM of The Wellcome Foundation) also composite **antibodies**, wherein parts of the hypervariable regions in addition to the CDRs are tranferred to the human framework. Additional amino acids in the framework or constant regions of such **antibodies** may be altered. The invention further includes the production of Fab fragments which are roughly equivalent to the Y branch. . .

DETDESC:

DETD(10)

C1H . . . 77, 7 p 4216-4220). CHO DUK B11 cells cannot produce dihydrofolate reductase (dhfr). These cells were engineered to produce a **humanized** IgG **antibody**, **Campath** 1H (Winter et al., Nature, 1988, 322, 323-327), using plasmid constructs to express heavy and light **antibody** chains and the mouse dhfr. Expression is amplified and maintained using the folate antagonist methotrate. C1H 3D11* cells growing as. . .

US PAT NO:	5,786,176 [IMAGE AVAILABLE]	L1: 12 of 21
DATE ISSUED:	Jul. 28, 1998	
TITLE:	Recombinant CDw52 antigen	
INVENTOR:	Geoffrey Hale, Cambridge, Great Britain Herman Waldmann, Oxford, Great Britain Masahide Tone, Cambridge, Great Britain John Tite, Breckenham, Great Britain Christine Hale, Breckenham, Great Britain	
ASSIGNEE:	British Technology Group Limited, London, England (foreign corp.)	
APPL-NO:	08/374,533	
DATE FILED:	Feb. 3, 1995	
PCT-FILED:	Jul. 14, 1993	
PCT-NO:	PCT/GB93/01482	
371-DATE:	Feb. 3, 1995	
102(E)-DATE:	Feb. 3, 1995	
PCT-PUB-NO:	WO94/02604	
PCT-PUB-DATE:	Feb. 3, 1994	
FRN-PRIOR:	United Kingdom 9215071	Jul. 15, 1992
INT-CL:	[6] C12N 15/09	
US-CL-ISSUED:	435/69.3, 172.3, 352, 362	
US-CL-CURRENT:	435/69.3, 352, 362	
SEARCH-FLD:	435/7.21, 7.24, 7.95, 69.3, 172.3, 240.2, 325, 352, 362,	

US PAT NO: 5,654,403 [IMAGE AVAILABLE] L1: 15 of 21
DATE ISSUED: Aug. 5, 1997
TITLE: Immunoglobulins stabilized with a chelator of copper ions
INVENTOR: Marjorie Smith, Beckenham, Great Britain
Valentina Riveros-Rojas, Beckenham, Great Britain
ASSIGNEE: Burroughs Wellcome Co., Research Triangle Park, NC (U.S. corp.)
APPL-NO: 08/232,127
DATE FILED: Apr. 28, 1994
PCT-FILED: Oct. 27, 1992
PCT-NO: PCT/GB92/01970
371-DATE: Apr. 28, 1994
102(E)-DATE: Apr. 28, 1994
PCT-PUB-NO: WO93/08837
PCT-PUB-DATE: May 13, 1993
FRN-PRIOR: United Kingdom 9122820 Oct. 28, 1991
INT-CL: [6] C07K 16/00; C07K 16/28; C07K 16/30
US-CL-ISSUED: 530/387.3, 387.7, 388.73, 388.75, 388.8, 390.5; 424/133.1
US-CL-CURRENT: 530/387.3; 424/133.1; 530/387.7, 388.73, 388.75, 388.8, 390.5
SEARCH-FLD: 530/387.3, 390.5, 387.7, 388.73, 388.75, 388.8; 424/133.1
REF-CITED:

U.S. PATENT DOCUMENTS

4,722,899	2/1988	Hamaoka et al.	435/172.2
5,087,695	2/1992	McAuley	530/412
5,367,060	11/1994	Vandlen et al.	530/399

FOREIGN PATENT DOCUMENTS

0391526	10/1990	European Patent Office
0481790	4/1992	European Patent Office
9109967	7/1991	World Intellectual Property Organization

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Velander et al., Biotechnology Progress, vol. 5, No. 3,pp. 119-125. (1989).
Chvapil et al., Biochemical Pharmacology, vol. 21, pp. 1097-1651, 1972.
Borrebaeck, Journal of Immunological Methods, vol. 123, pp. 157-165 (1989).
Harris et al., TIBTECH, vol. 11, pp. 42-44, (1993).
Bach et al., Immunology Today, vol. 14, No. 9, pp. 421-425. (1993).
Waldmann, Science, vol. 252, pp. 1657-1662, (1991).
Seaver, Genetic Engineering News, pp. 10 and 21 (1994).
Osband et al., Immunology Today, vol. 11, No. 6, pp. 193-195 (1990).
Baker et al., Biol. Chem., vol. 253, pp. 844-845, (1978).
Riechmann et al., Nature, vol. 332, pp. 323-327 (1988).
ART-UNIT: 186
PRIM-EXMR: Toni R. Scheiner
LEGAL-REP: Rothwell, Figg, Ernst & Kurz

ABSTRACT:

A stabilized immunoglobulin composition comprises at least one immunoglobulin together with a stabilizing amount of a chelator of copper ions such as EDTA or citrate. Preferably the immunoglobulin is an antibody, for example, a recombinant CDR-grafted antibody. A process for enhancing the stability of an immunoglobulin comprises subjecting the immunoglobulin to a purification procedure capable of removing copper ions therefrom. Preferably, the immunoglobulin is rendered substantially

free from detectable cop ions as determined, for examp by atomic absorption spectroscopy.

16 Claims, No Drawings

US PAT NO: 5,644,036 [IMAGE AVAILABLE] L1: 16 of 21
DATE ISSUED: Jul. 1, 1997
TITLE: Purified immunoglobulin
INVENTOR: Paul Ian Nicholas Ramage, Reinach, Switzerland
Geoffrey Allen, Beckenham, England
ASSIGNEE: Burroughs Wellcome Company, Research Triangle Park, NC (U.S. corp.)
APPL-NO: 08/319,598
DATE FILED: Oct. 7, 1994
REL-US-DATA: Continuation of Ser. No. 304,440, Sep. 12, 1994, which is a continuation of Ser. No. 985,272, Dec. 3, 1992, abandoned, which is a continuation of Ser. No. 975,967, Nov. 13, 1992, abandoned, which is a continuation of Ser. No. 777,731, Oct. 16, 1991.
FRN-PRIOR: United Kingdom 9022547-5 Oct. 17, 1990
INT-CL: [6] C07K 1/18; C07K 1/22; C07K 1/36
US-CL-ISSUED: 530/412; 435/69.6; 530/413, 416, 417
US-CL-CURRENT: 530/412; 435/69.6; 530/413, 416, 417
SEARCH-FLD: 435/240.1, 240.27; 530/412, 413, 416, 417
REF-CITED:

FOREIGN PATENT DOCUMENTS

0328404	2/1989	European Patent Office
8905157	6/1989	World Intellectual Property Organization

OTHER PUBLICATIONS

Lambert et al. [J. Biol. Chem. 260(22):12035-12041 (1985)].
Lambert et al. [Cancer Treat Res 37:323-348 (1988)].

H

US PAT NO: 5,633,162 [IMAGE AVAILABLE] L1: 17 of 21
DATE ISSUED: May 27, 1997
TITLE: Method for culturing Chinese hamster ovary cells
INVENTOR: Michael J. Keen, Beckenham, England
Nicholas T. Rapson, Beckenham, England
ASSIGNEE: Glaxo Wellcome Inc., Research Triangle Park, NC (U.S. corp.)
APPL-NO: 08/205,379
DATE FILED: Mar. 4, 1994
REL-US-DATA: Continuation of Ser. No. 991,717, Dec. 18, 1992, Pat. No. 5,316,938, which is a continuation of Ser. No. 777,729, Oct. 16, 1991, abandoned.
FRN-PRIOR: United Kingdom 9022545 Oct. 17, 1990
INT-CL: [6] C12N 5/00
US-CL-ISSUED: 435/384, 386, 387
US-CL-CURRENT: 435/384, 386, 387
SEARCH-FLD: 435/240.1, 240.3, 240.31
R

US PAT NO: 5,792,838 [IMAGE AVAILABLE] L1: 11 of 21
DATE ISSUED: Aug. 11, 1998
TITLE: Method for stabilizing immunoglobulin compositions
INVENTOR: Marjorie Smith, Beckenham, Great Britain
Valentina Riveros-Rojas, Beckenham, Great Britain
ASSIGNEE: Glaxo Wellcome Inc., Research Triangle Park, NC (U.S. corp.)
APPL-NO: 08/465,319
DATE FILED: Jun. 5, 1995
REL-US-DATA: Continuation of Ser. No. 232,127, Apr. 28, 1994.
FRN-PRIOR: United Kingdom 9122820 Oct. 28, 1991
INT-CL: [6] C07K 16/00
US-CL-ISSUED: 530/387.1, 387.3, 388.1, 389.1
US-CL-CURRENT: 530/387.1, 387.3, 388.1, 389.1
SEARCH-FLD: 530/387.1, 388.1, 389.1, 387.3
REF-CITED:

U.S. PATENT DOCUMENTS

2,149,304	3/1939	Masucci	
4,722,899	2/1988	Hamaoka et al.	435/172.2
5,087,695	2/1992	McAuley	530/412
5,367,060	11/1994	Vandlen et al.	530/399

US PAT NO: 5,792,838 [IMAGE AVAILABLE] L1: 11 of 21
DATE ISSUED: Aug. 11, 1998
TITLE: Method for stabilizing immunoglobulin compositions
INVENTOR: Marjorie Smith, Beckenham, Great Britain
Valentina Riveros-Rojas, Beckenham, Great Britain
ASSIGNEE: Glaxo Wellcome Inc., Research Triangle Park, NC (U.S. corp.)
APPL-NO: 08/465,319
DATE FILED: Jun. 5, 1995
REL-US-DATA: Continuation of Ser. No. 232,127, Apr. 28, 1994.
FRN-PRIOR: United Kingdom 9122820 Oct. 28, 1991
INT-CL: [6] C07K 16/00
US-CL-ISSUED: 530/387.1, 387.3, 388.1, 389.1
US-CL-CURRENT: 530/387.1, 387.3, 388.1, 389.1
SEARCH-FLD: 530/387.1, 388.1, 389.1, 387.3
REF-CITED:

U.S. PATENT DOCUMENTS

2,149,304	3/1939	Masucci	
4,722,899	2/1988	Hamaoka et al.	435/172.2
5,087,695	2/1992	McAuley	530/412
5,367,060	11/1994	Vandlen et al.	530/399